REMARKS

Claims 1, 3-10, 12-18, 20, and 23-31 are pending. The language of claim 1 has been slightly rearranged to improve its format and to clarify that the core material is not coated with a separating layer. This amendment has been added in response to the examiner's interpretation that the previous claims allowed for the inclusion of a separating layer. Although applicants disagree with the examiner's interpretation of the previous claims and believe the additional language is not necessary, it has been added to expedite prosecution and/or reduce the issues for appeal. Explicit support for the recitation is located on page 3, lines 27-29 of the specification and in the examples (none of the examples include a separating layer). Applicants amended claims 9-10, 12, and 30 without prejudice or disclaimer and merely for purposes of clarification to replace the term "alkaline additive" to "alkalizing additive" to ensure proper antecedent basis in claim 1. Applicants have changed the phase "a semipermeable membrane" in claim 20 without prejudice or disclaimer and merely for purposes of clarification to "the semipermeable membrane" to ensure proper antecedent basis in claim 1. No new matter has been added into the claims.

Response to Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1, 3-10, 12-18, 20 and 23-31 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Specifically, the claims stand rejected for providing that the outermost layer of the dosage form is a semipermeable membrane. While not agreeing with the merit or substance of the rejection and merely to further prosecution, applicants have amended the claims without prejudice or disclaimer to clarify that the core material is coated with a semipermeable membrane. Support for this recitation is located in the specification, for example, on page 3, lines 15-16. In view of the amendment, the rejection no longer applies and should be withdrawn.

Response to Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 3-10, 12-18, 20 and 23-31 have been rejected under 35 U.S.C. § 112, second paragraph as indefinite. According to the rejection, it is not clear what the claim is referring to where it recites that the outermost layer of the dosage form is a semipermeable membrane. While not agreeing with the merit or substance of the rejection and merely to further prosecution, applicants have amended the claims without prejudice or disclaimer to clarify that the core material is coated with a semipermeable membrane as discussed above. Accordingly, the rejection no longer applies and should be withdrawn.

Response to Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3, 6-8, 12-18, 20 and 25-29 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Nara *et al.*, U.S. Patent No. 6,245,351 ("Nara *et al.*") in view of Bergstrand *et al.*, U.S. Patent No. 5,753,265 ("Bergstrand *et al.*").

The rejection is improper because:

1. The references do not account for every element of the claims;

2. The references teach away from proceeding as applicants have done; and

3. Evidence of unexpected results exists.

The references do not account for a semipermeable membrane comprising a single polymer composition. To establish *prima facie* obviousness, all the claim limitations must be accounted for. The Board of Patent Appeals and Interferences recently stated:

> When determining whether a claim is obvious, an examiner must make a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Moreover, as the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of

> obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

In re Wada and Murphy, Appeal 2007-3733 (Bd. Pat. App. & Inter. 2008).

As pointed out in applicants' March 7, 2008 response, Nara *et al.* describes a core material coated with a polymer composition containing two or three polymers, *i.e.*, a water insoluble polymer, a swellable polymer; and an optional hydrophilic substance. *See* column 6, lines 16-21, claims 1 and 9, and Examples 1-11. Nara *et al.* also describes a separating layer formed by a polymer in column 6, lines 1-10. If this polymer coating is also considered, Nara *et al.* actually describes a core material coated with as many as four polymers. The instant claims, however, are directed to a core material coated with a single polymer composition.

In the September 4, 2008 Office Action, the examiner determined that the separating layer of Nara *et al.* was equivalent to the single polymer composition of applicants' claims as a basis to maintain the obviousness rejection. *See* Sept. 4, 2008 Office Action, p. 10, lines 20-21. The examiner did not consider that the separating layer of Nara *et al.* is further coated with the multi-polymer coating composition described in column 6, lines 15-21. Nowhere in Nara *et al.* does it teach coating a core material with only a separating layer or only a single polymer composition. Nonetheless, in response to the examiner's claim interpretation, applicants have amended the claims to state that "the core material is not coated with a separating layer." As explained above, express support for this recitation is located in the specification on page 3, lines 27-29 and in the examples.

In view of the amendment, the rejection cannot stand because it does not account for a semipermeable membrane comprising a single polymer composition (wherein the single polymer composition is not a separating layer). Furthermore, as explained more fully below, there is no reason why one of skill in the art would modify the teachings of Nara *et al.* to exclude a separating layer and the multiple-polymer coating of Nara *et al.* (or the enteric coating of Bergstrand *et al.*).

The cited references teach away from coating a core material with only a single polymer composition. Where a reference teaches away from and discourages a person skilled in the art from doing what is claimed, the reference established "the very antithesis of obviousness." *In re Buehler* 185 USPQ 781 (CCPA 1975). The prior art "must be considered in its entirety, including disclosures that teach away from the claims." MPEP § 2141.02(IV); *see also, e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). The references cited in the rejection illustrate the "teaching away" in the art. These references teach that omeprazole should be coated with an enteric coating or by multiple polymers.

- Bergstrand *et al.* explains that H^+K^+-ATPase inhibitors such as omeprazole "are best protected from contact with acidic gastric juice by an enteric coating layer." *See* column 4, lines 5-7. It goes on to describe the inclusion of a separating layer in column 7, lines 43-50.

- Lundberg *et al.*, U.S. Patent No. 6,013,281 ("Lundberg *et al.*") is directed to an enteric coated pharmaceutical dosage form of omeprazole. *See, e.g.*, claim 3 and example 2. It also describes including a separating layer. *See, e.g.*, the abstract.

- Hodges *et al.*, U.S. Patent No. 5,225,202 ("Hodges *et al.*") is directed to an enteric coated pharmaceutical composition for a medicament that is sensitive to a low pH environment. *See* the abstract. It describes using a "subcoat layer" to act as a physical barrier between the core and outer enteric coating layer in column 4, lines 59-65.

- Nara *et al.* is directed to a controlled-release composition formed by coating a core material with multiple polymers. *See, e.g.,* the abstract. The specification lists examples of drugs that may be employed in the controlled-release composition in column 3, lines 34-64, reproduced below.

> Examples of the drug for the present invention include, but are not limited to, opioid compounds such as morphine or pharmacologically acceptable salts thereof (e.g., hydrochloride, sulfate), hydromorphone,

> oxycodone, methadone, meperidine, dihydrocodeine, codeine, dihydromorphine, buprenorphine and fentanyl; antiinflammatory agents such as Naploxen Na, isopropylantipyrine HCl, ibuprofen, ketoprofen, diclofenac Na; sympathomimetics such as ephedrine HCl, salbutamol sulfate, terbutaline sulfate and phenylpropanolamine HCl; anti-allergic drugs such as phenylamine and terfenadine; antihystamines such as chlorpheniramine maleate, diphenhydramine HCl and clemastine fumarate; cardiac drugs such as procainamide hydrochloride, propranolol hydrochloride and quinidine sulfate; antihypertensive drugs such as metoprolol, captopril, hydralazin HCl and diltiazem HCl; antibiotics such as Penicillin V Potassium, Cloxacillin Na, Metronidazole hydrochloride, amoxicillin, cephalexin and clarithromycin; bronchodilators such as theophylline and salbutamol; anti-arrhythmic drugs such as procainamide and quinidine; antineoplastics such as flutamide and fluorouracil; anticonvulsants such as phenytoine Na, ethosuximide and valproate Na; central nervous-acting substances such as chlopromazine hydrochloride, diazepam and perphenazine; gastrointestinal agents such as ranitidine HCl, cimetidine famotidine, ***omeprazole*** and lansoprazole; antidiabetic agents such as acarbose voglibose and tolbutamide; cholinergir agent such as bethanecol chloride, neostigumine bromide and carbachol; vitamins; amino acids; and peptides (emphasis added).

Omeprazole is but one of many compounds in this large laundry list of diverse drug substances and is not exemplified in any examples or even mentioned again within the entire disclosure of Nara *et al.* Instead, Nara *et al.* repeatedly exemplifies morphine hydrochloride and phenylpropanolamine hydrochloride. A prior art reference that teaches or suggests a preferred embodiment different from the claimed subject matter weighs against a determination of obviousness. *In re Baird*, 16 F.3d 380, 82-83, (Fed. Cir. 1994); *See also* MPEP 2144.08(II)(A)(4).

Assuming one would select omeprazole from this long list, Nara *et al.* teaches that the core material should be coated with multiple polymers—not just one polymer as recited by the instant claims. Nara *et al.* describes a core material coated with a polymer composition containing two, three, or even four polymers, *i.e.*, a water insoluble polymer, a swellable polymer, an optional hydrophilic substance, and a protective layer. *See* column 6, lines 1-10 and 16-21, claims 1 and 9, and Examples 1-11. Thus, the art of record explicitly teaches those of

skill in the art to coat omeprazole with an enteric coating or with multiple polymers. Here, applicants did neither but proceeded contrary to the teachings of the art. Applicants developed a dosage form that eliminates the need for an enteric or multiple-polymer coating. Furthermore, as explained below, applicants discovered that contrary to the teachings of the prior art, the claimed dosage form unexpectedly improves the delivery of omeprazole.

The claimed omeprazole core coated with a single polymer composition shows unexpected results providing objective evidence of nonobviousness. The Supreme Court recently affirmed the importance of "secondary considerations" in the determination of obviousness. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1730 (2007). "[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983); MPEP 716.01(a).

In a side-by-side comparison with the examples from Nara *et al.* (the reference the examiner deems the closest prior art), the data show that the claimed single polymer coated cores unexpectedly perform better at both the low pH of the stomach (pH of ~1.0) and at the higher pH of the gastrointestinal tract (pH of ~6.8).

Nara *et al.* provides dissolution data for Examples 1 and 9 for dosage forms of morphine and presents the testing results in Figures 1 and 2. *See* Example 1, Example 9, Experimental Example 1, Experimental Example 2, and column 13, lines 2-38. In these two examples the drug core is first coated with a polymer separating layer of HPMC and then coated with a multi-polymer coating of (1) a water insoluble polymeric component of ethyl cellulose, (2) a crosslinked polyacrylate polymer/HIVISWAK, and (3) a hydrophilic polymer of HPMC.

Example 4 in the instant specification provides dissolution data for an omeprazole core coated with a single polymer composition (ethyl cellulose) in accordance with the instant claims. After two hours in 0.1 M HCl (pH = 1), only **4% of the drug was released**. In contrast, Figure 2 of Nara *et al.* shows that about **10% the drug was released** after two hours at a pH of 1.2. Figure 1 shows results similar to applicants' results. Release of omeprazole is undesirable at a

low pH because it is quickly destroyed. The data described above shows that at a low pH, the claimed drug core coated with a single polymer composition is equivalent to or better than the multi-polymer coated cores of Nara *et al.* in preventing release of the drug.

At a higher pH omeprazole should quickly release to exhibit a therapeutic effect on the body. Page 14 of the instant specification shows that after two hours at a pH of 6.8, **60% of drug was released**. In contrast, Figure 1 of Nara *et al.* shows that only about **5% of drug was released** after two hours at a pH of 6.8. Figure 2 shows that about 40% of drug was released after two hours at a pH of 6.8. Thus, at a higher pH, the data shows that the claimed omeprazole core coated with a single polymer composition is consistently and significantly faster at releasing the drug substance than the multi-polymer coated cores of Nara *et al.* The above results are surprising and unexpected, especially considering that the art teaches that omeprazole should have an enteric coating or a multiple polymer coating to prevent release of the drug at a low pH and to promote release of the drug at a higher pH.

In sum, the rejection is improper because the references do not account for an omeprazole core coated with a single polymer composition (wherein the single polymer composition is not a separating layer), the references teach away from proceeding as applicants have done, and evidence of unexpected results exist. Accordingly, the rejection should be withdrawn.

Claims 30-31 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Nara *et al.* in view of Bergstrand *et al.* and Hodges *et al.* As pointed out above, Hodges *et al.* teaches away from proceeding as applicants have done by teaching that an active ingredient sensitive to a low pH should have an enteric coating. *See* the abstract. Additionally, Hodges *et al.* describes using a "subcoat layer" to act as a physical barrier between the core and outer enteric coating layer in column 4, lines 59-65. Furthermore, Hodges *et al.* does not describe an omeprazole core coated with a single polymer composition. Therefore, the rejection is improper and should be withdrawn for the reasons set forth above, which are incorporated herein by reference in their entirety.

Claims 9-10 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Nara *et al.* in view of Bergstrand *et al.* and Zentner, U.S. Patent No. 4,795,644 ("Zentner") or Lundberg *et al.*, U.S. Patent No. 6,013,281 ("Lundberg *et al.*"). Zentner has been cited to show that mono- and di-phosphates are pH modifying agents and Lundberg *et al.* has been cited to show that arginine may be an alkalizing additive. Neither reference negates the teaching away of Nara *et al.* and Bergstrand *et al.* nor do they describe an omeprazole core coated with a single polymer composition. Therefore, the rejection of claims 9-10 is improper and should be withdrawn for the reasons set forth above, which are incorporated herein by reference in their entirety.

Claims 4-5 and 23-26 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Nara *et al.* in view of Bergstrand *et al.* and Cotton *et al.*, WO 98/54171 ("Cotton *et al.*"). Cotton *et al.* has been cited to show a highly crystalline magnesium salt of S-omeprazole trihydrate. Cotton *et al.* does not negate the teaching away of Nara *et al.* and Bergstrand *et al.* nor does it describe an omeprazole core coated with a single polymer composition. Therefore, the rejection of claims 9-10 is improper and should be withdrawn for the reasons set forth above, which are incorporated herein by reference in their entirety.

In view of the above, consideration and allowance are respectfully solicited.

In the event the Examiner believes an interview might serve in any way to advance the prosecution of this application, the undersigned attorney is available at the telephone number noted below.

The Office is authorized to charge any necessary fees to Deposit Account No. 22-0185.

This response is being submitted with the fee and a petition for a five month extension of time. Applicant believes no additional fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 22-0185, under Order No. 15652-00020-US from which the undersigned is authorized to draw.

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